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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/986,174	11/07/2001	Nabil Hanna	037003-0280732	4956

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
04/03/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket_ip@pillsburylaw.com

Office Action Summary	Application No.	Applicant(s)	
	09/986,174	HANNA, NABIL	
	Examiner	Art Unit	
	MISOOK YU	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16 and 23-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16 and 23-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

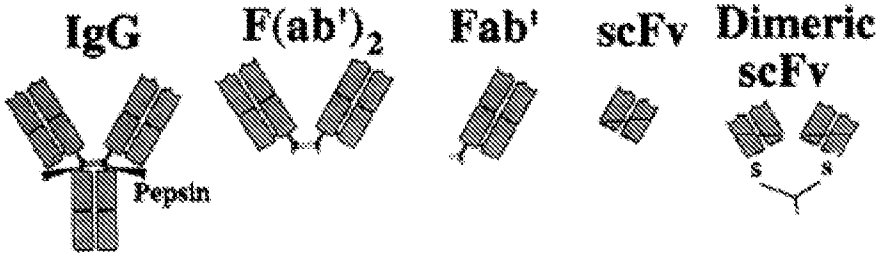
A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/31/2007 has been entered. The rejection of record is withdrawn because applicant's argument is considered to be persuasive.The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 16 and 23-38 are pending and examined on merits.

Claim Rejections - 35 USC § 112

Claims 16 and 23-38 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for rituximab, does not reasonably provide enablement for any other fragments and/or recited murine antibody with murine constant regions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 16 defines the term "immunogenic fragment" as fragment of an anti-CD 20 antibody that binds to CD20 expressed by a B cell lymphoma cell. However, claim 26 says that the term "immunogenic fragment" is "a single variable regions of the anti-CD20 antibody VL or VH, two or more variable regions, domain deleted antibody". The

specification does not disclose any new anti-body fragments and new technology. The state of antibody art, for example, Shan et al., (IDS NNNR filed on 11/10/2004, 1999, J. Immunol. 162, pages 6589-95) teach "the smallest Ab fragment that still contains the entire Ag binding site is the Fv fragment, consisting of the variable domains of the heavy (V_H) and light (V_L) chains as shown in Fig. 1 of Shan et al., below.



Therefore, one of skilled in the art would have a reason to doubt that the claimed "a single variable regions of the anti-CD20 antibody VL or VH, two or more variable regions, domain deleted antibody" would binds to CD20 since an antigen binding requires a minimum of Fv fragment, consisting of the variable domains of the heavy (V_H) and light (V_L) chains as taught by Shan et al.

In addition, the claimed invention is not enabled because the base claims 16 and 29 both say that the claimed antibody or fragments possess human effector function. Reff et al., (IDS filed on 11/10/2004, 1994, Blood vol. 83, 435-445) teaches on page 435 right column "unlike murine antibody, the chimeric antibody binds human C1q, and mediates a complement-dependent cell lysis (CDCC) in the presence of human complement, and antibody-dependent cellular cytotoxicity (ADCC) with human effector cells." Thus, Reff et al., teach human constant chains of antibody is necessary in order

to have the claimed human effector functions since the murine counter part did not have the human effector function. Shan et al., (cited above) teach IF5 is murine antibody. Other antibodies or antibody fragments except rituximab would not have the required human effector function since they do not have necessary structures. Note also US 6455043 B1 discloses that ibritumomab is murine counter part to rituximab.

Based on the state of the art, one of skill in the art would have a reason to doubt that an antibody fragment consisting of only VL or VH (not the construction of claim 26, for example), or murine monoclonal antibody would have human effector function.

Claim Rejections - 35 USC § 103

Claims 16 and 23-31, 33, and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al of record in view of Ozzello et al (IDS filed on 06/14/2004, 1993, Breast Cancer Research and Treatment, vol. 25, pages 263-276).

The claimed invention is drawn to method of treating B cell lymphoma comprising administering to a subject an immunoconjuate comprising an anti-CD20 antibody and interferon-alpha-2a

Davis et al., teach at page 2645, right column that an anti-CD20 antibody (i.e., Rituximab) and IFN had synergistic effect on preclinical trials, therefore the authors of the study set out to do the human clinical trials, and found that the combination therapy between anti-CD20 antibody, and interferon alpha 2a had a good result in humans as well. Davis et al., at page 2644 also teach “Rituximab is a mouse/human chimeric antibody containing human constant regions (IgG1 k isotype) and murine variable regions”; This suggests that making a recombinant antibody, or attaching other protein

to a recombinant antibody at its carboxy terminal is well within the skill of an ordinary artisan before the effective filing date of the instant application. Davis et al., at 1st line of abstract teach “Rituximab and IFN have each demonstrated single-agent activity in patients with low-grade non-Hodgkin's lymphoma (NHL)”, and also teach "efficacy of combination therapy with rituximab and IFN-alpha-2a” is started because each of two active agents in the instant claims had shown efficacy in treating a B cell lymphoma. Davis et al., at 1st paragraph under Discussion on page 2649 teach “IFN-α has pleiotropic effects on the immune system, including increased expression of the MHC class I antigen, cellular adhesion molecules and other tumor antigens, increased production of, and sensitivity to, other cytokines, as well as augmentation of the cytotoxic activity of NK cells, an integral part of ADCC (56 , 57) . Although the predominant mechanism of action of rituximab *in vivo* is not known, the antibody is able to mediate both complement and antibody-mediated cell killing (ADCC; Ref. 10). Evidence that IFN-α could stimulate the ability of NK cells to mediate ADCC (58) suggests that simultaneous treatment with IFN-α and antibody may augment efficacy. The regimen used in this trial provided tolerable dosing of IFN-α before, during, and after rituximab therapy to maximize any synergistic activity.” Therefore the effector function recited in claim 23 and ADCC medicated cell lysis in claim 24 are the inherent functional characteristics of the antibody and/or IFN-alpha-2a taught by Davis et al. As for ibritumomab, US 6455043 B1 discloses that ibritumomab is murine counter part to rituximab as taught in Davis et al., therefore one of ordinary skill in the art would have known how to make the fusion protein using ibritumomab.

Ozzello et al., is cited to address applicant's earlier argument during the prosecution of this case that the claimed invention is not obvious because the dosage of IFN-alpha-2a is 1,600-fold less than that of the antibody in Davis et al., therefore one of ordinary skill in the art would not have been able to practice the invention with a reasonable expectation of success, or not have been motivated to arrive at the claimed invention. Ozzello et al., on middle of page 274 teach "the amount of radio-labeled IFN still detectable in the tissues, especially tumors and kidneys, 4 hours after injection of ^{125}I-nIFNα/IgG1 was greater than in the group receiving ^{125}I-nIFNα alone, but smaller than in the mice injected with ^{125}I-nIFNα/Mc5." Ozzello et al ^{125}I-nIFNα/Mc5 is an immunoconjugate linking an interferon to monoclonal antibody expressed on a tumor cell. Ozzello et al., teach that one of ordinary skill in the art would know how to determine a therapeutically effective amount of an immunoconjugate as well as based on the efficacy of each component in said immunoconjugate. One of ordinary skill in the art would have been able using routine in vitro and in vivo methodologies used to establish effective doses of compounds including immunoconjugates, for example, Materials and methods on pages 266-267 in of Ozzello et al., which describe an in vitro screening assay used to determine therapeutic dosages. It appears that one of ordinary skill in the art is well-aware that a precise dose to be employed in the treatment of B cell lymphoma depends on the disease stage, age, sex, medical complications and weight of the individual to be treated, thus determination of an effective dose of the described immunoconjugates for the treatment of B cell lymphoma was routine for a skilled artisan. Therefore it would have been obvious to one of the ordinary skill in the

art to make and use an anti-CD20 antibody or a fragment thereof is fused at its carboxy terminus to IFN-alpha-2a in the method treating the lymphoma with a reasonable expectation of success since how to make recombinant interferon alfa-2a, and how to construct anti-CD20 antibody expression construct had been well known in the art before the effective filing date of the instant application. One of an ordinary skill would have been motivated to make the fusion to minimize the painful injections by giving one fusion protein instead of two separate injections, and/or purifying one protein instead of two proteins, thus reducing cost and saving time. In addition, Ozzello et al., teach the amount of an interferon required is much less when the interferon is conjugated to a monoclonal antibody binding to an antigen expressed on tumor cells.

Claims 25, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al of record in view of Ozzello et al (IDS filed on 06/14/2004, 1993, Breast Cancer Research and Treatment, vol. 25, pages 263-276) as applied to claim 16 and 29 and further in view of Shan et al., (IDS NNNR filed on 11/10/2004, 1999, J. Immunol. 162, pages 6589-95).

Shan et al., is cited because two references cited above do not teach the limitation "IF5", which had been known well before the effective filing date of the instant application. Therefore, it is obvious to one of skill in the art at the time the instant application was filed to make and use an immunoconjugate made up with IF5 and interferon for treating B cell lymphoma with a reasonable expectation of success. The motivation would be same as rituximab fused to interferon.

Claims 25, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al of record in view of Ozzello et al (IDS filed on 06/14/2004, 1993, Breast Cancer Research and Treatment, vol. 25, pages 263-276) as applied to claim 16 and 29 and further in view of Haisma et al., IDS IIR filed on 11/10/2004, 1998, Blood 92, 184-90

Haisma et al., is cited because two references cited above do not teach the limitation "1H4 single chain Fv antibody", which had been known well before the effective filing date of the instant application. Therefore, it is obvious to one of skill in the art at the time the instant application was filed to make and use an immunoconjugate made up with 1H4 single chain Fv antibody as taught by Haisma et al., and interferon for treating B cell lymphoma with a reasonable expectation of success.

Claims 25, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al of record in view of Ozzello et al (IDS filed on 06/14/2004, 1993, Breast Cancer Research and Treatment, vol. 25, pages 263-276) as applied to claim 16 and 29 and further in view of V0se et al., IDS filed on 06/12/2007, J. Clin. Oncol., (Abstract), March 2000.

Vose et al., is cited because two references cited above do not teach the limitation "tositumomab ", which had been known well before the effective filing date of the instant application. Vose et al., teach iodine-131 tositumomab are effective for B-cell non-Hodgkin's lymphoma.

Therefore, it is obvious to one of skill in the art at the time the instant application was filed to make and use an immunoconjugate made up with tositumomab as taught

by Vose et al., and interferon for treating B cell lymphoma with a reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Primary Examiner
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